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EXAMINER
KERR, KATHLEEN M

ART UNIT	PAPER NUMBER
1652	15

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Please find below and/or attached an Office communication concerning this application or proceeding.

SM.

Office Action Summary	Application No. 09/836,705	Applicant(s) ABE ET AL.	
	Examiner Kathleen M Kerr	Art Unit 1652	

-- The MAILING DATE of this communication appears on the cover sheet with the correspondence address --

Period for Reply

A SHORTENED STATUTORY PERIOD FOR REPLY IS SET TO EXPIRE 3 MONTH(S) FROM THE MAILING DATE OF THIS COMMUNICATION.

- Extensions of time may be available under the provisions of 37 CFR 1.136(a). In no event, however, may a reply be timely filed after SIX (6) MONTHS from the mailing date of this communication.
- If the period for reply specified above is less than thirty (30) days, a reply within the statutory minimum of thirty (30) days will be considered timely.
- If NO period for reply is specified above, the maximum statutory period will apply and will expire SIX (6) MONTHS from the mailing date of this communication.
- Failure to reply within the set or extended period for reply will, by statute, cause the application to become ABANDONED (35 U.S.C. § 133).
- Any reply received by the Office later than three months after the mailing date of this communication, even if timely filed, may reduce any earned patent term adjustment. See 37 CFR 1.704(b).

Status

1)☒ Responsive to communication(s) filed on *12 March 2003* .

2a)☐ This action is **FINAL**. 2b)☒ This action is non-final.

3)☐ Since this application is in condition for allowance except for formal matters, prosecution as to the merits is closed in accordance with the practice under *Ex parte Quayle*, 1935 C.D. 11, 453 O.G. 213.

Disposition of Claims

4)☒ Claim(s) *1-55* is/are pending in the application.

4a) Of the above claim(s) *1-39,44 and 46-55* is/are withdrawn from consideration.

5)☐ Claim(s) _____ is/are allowed.

6)☒ Claim(s) *40-43 and 45* is/are rejected.

7)☐ Claim(s) _____ is/are objected to.

8)☐ Claim(s) _____ are subject to restriction and/or election requirement.

Application Papers

9)☒ The specification is objected to by the Examiner.

10)☐ The drawing(s) filed on _____ is/are: a)☐ accepted or b)☐ objected to by the Examiner.

Applicant may not request that any objection to the drawing(s) be held in abeyance. See 37 CFR 1.85(a).

11)☐ The proposed drawing correction filed on _____ is: a)☐ approved b)☐ disapproved by the Examiner.

If approved, corrected drawings are required in reply to this Office action.

12)☐ The oath or declaration is objected to by the Examiner.

Priority under 35 U.S.C. §§ 119 and 120

13)☒ Acknowledgment is made of a claim for foreign priority under 35 U.S.C. § 119(a)-(d) or (f).

a)☒ All b)☐ Some * c)☐ None of:

1.☒ Certified copies of the priority documents have been received.

2.☐ Certified copies of the priority documents have been received in Application No. _____ .

3.☐ Copies of the certified copies of the priority documents have been received in this National Stage application from the International Bureau (PCT Rule 17.2(a)).

* See the attached detailed Office action for a list of the certified copies not received.

14)☐ Acknowledgment is made of a claim for domestic priority under 35 U.S.C. § 119(e) (to a provisional application).

a) ☐ The translation of the foreign language provisional application has been received.

15)☐ Acknowledgment is made of a claim for domestic priority under 35 U.S.C. §§ 120 and/or 121.

Attachment(s)

1) ☒ Notice of References Cited (PTO-892)
2) ☐ Notice of Draftsperson's Patent Drawing Review (PTO-948)
3) ☒ Information Disclosure Statement(s) (PTO-1449) Paper No(s) *12* .
4) ☐ Interview Summary (PTO-413) Paper No(s). _____ .
5) ☐ Notice of Informal Patent Application (PTO-152)
6) ☒ Other: *sequence alignment* .

DETAILED ACTION

Application Status

1. In response to the previous Office action, a written restriction requirement (Paper No. 13, mailed on February 19, 2003), Applicants filed an election received on March 12, 2003 (Paper No. 14). Thus, Claims 1-55 are pending in the instant Office action.

Election

2. Applicant's election with traverse of Group VI (Claims 40-43 and 45) in Paper No. 14 is acknowledged. The traversal is on the ground(s) that the claims are classified in the same class (either 435 or 530). This is not found persuasive because searching more than one subclass presents and undue burden on the Examiner due to the enormous amount of publications in each subclass within the classes. As noted in M.P.E.P. § 803, "[f]or purposes of the initial requirement, a serious burden on the examiner may be *prima facie* shown if the examiner shows by appropriate explanation of separate classification, or separate status in the art, or a different field of search as defined in M.P.E.P. § 808.02".

The traversal is also on the ground(s) that different Groups are drawn to the same claims and that Markush group has been divided. This is not found persuasive because in Claim 1, for example, the two members are not species of a common genus with a special feature free of the prior art as required by Markush practice. In M.P.E.P. § 803.02, "A Markush-type claim can include independent and distinct inventions. This is true where two or more of the members are so unrelated and diverse that a prior art reference anticipating the claim with respect to one of the members would not render the claim obvious under 35 U.S.C. 103 with respect to the other

member(s)." The only thing in common between the two genes is that they are both polynucleotides from the same source species and their encoded proteins are involved in ML-236B biosynthesis. However, the functions of these two genes (and their encoded proteins) are wholly distinct as clearly evidenced by the distinct grouping (class/subclass) of this subject matter. Moreover, art against one of the polynucleotides would in no way constitute art against the other requiring wholly separate searches as previously noted.

The requirement is still deemed proper and is therefore made FINAL.

Claims 1-55 are pending in the instant application. Claims 1-39, 44, and 46-55 are withdrawn from consideration as non-elected inventions. Claims 40-43 and 45 will be examined herein.

Priority

3. The instant application is granted the benefit of priority for the foreign application 2000-116591 filed in Japan on April 18, 2000 and 2000-117458 filed in Japan on April 19, 2000 as requested in the declaration.

Receipt is acknowledged of papers submitted under 35 U.S.C. § 119(a)-(d), which papers have been placed of record in the file. Said papers are not in English; no English translations have been filed.

Information Disclosure Statement

4. The references noted in the information disclosure statement filed on October 25, 2001 (Paper No. 8) cannot be located. Applicants are required to submit copies of said references in response to the instant Office action, at which time, said references will be considered.

5. The information disclosure statement filed on February 12, 2002 (Paper No. 12) has been reviewed, and its references have been considered as shown by the Examiner's initials next to each citation on the attached copy.

Drawings

6. The drawings have been approved by the Draftsmen and are, therefore, entered as formal drawings acceptable for publication upon the identification of allowable subject matter. The originally filed application, including the drawings, has been published in USPAP 2003/0078395 on April 24, 2003.

Sequence Compliance

7. By virtue of Applicants' filing an amended sequence listing on October 25, 2001 (Paper No. 5), the instant application now fully complies with the sequence rules.

Objections to the Specification

8. The specification is objected to because the title is not descriptive. A new title is required that is clearly indicative of the invention to which the elected claims are drawn (see M.P.E.P. § 606.01). The Examiner suggests the following new title:

---Methods for Producing ML-236B, a Pravastatin Precursor, Using a Host Cell Transformed with *mlcR*, a Transcription Factor---

9. In the specification, the Abstract is objected to for not completely describing the disclosed subject matter (see M.P.E.P. § 608.01(b)). It is noted that in many databases and in foreign countries, the Abstract is crucial in defining the disclosed subject matter, thus, its

completeness is essential. The Examiner suggests the inclusion of the source of the genes disclosed, *Penicillium citrinum*, as well as the names of the genes: *mlcE*, an efflux pump, and *mlcR*, and transcription factor, in the gene cluster disclosed. Correction is required.

Claim Objections

10. Claims 40-43 and 45 are objected to for depending from non-elected Claims 29, 27, 26, and 1. The limitations of Claims 29, 27 and/or 26, and 1 must be inserted into Claim 40.

11. Claims 40-43 and 45 are objected to for containing non-elected subject matter. Claim 1 contains non-elected subject matter, thus, only a portion of Claim 1 (item b) will be read into the examined claims. Claim 27 contains non-elected subject matter, thus, only a portion of Claim 1 (relating to pSAKexpR) will be read into the examined claims.

Also, in Claim 41, the reference to SEQ ID NO:37 must be deleted as a non-elected invention.

Claim Rejections - 35 U.S.C. § 112

The following is a quotation of the second paragraph of 35 U.S.C. § 112:

> The specification shall conclude with one or more claims particularly pointing out and distinctly claiming the subject matter which the applicant regards as his invention.

12. Claims 40, 42-43 and 45 are rejected under 35 U.S.C. § 112, second paragraph, as being indefinite for failing to particularly point out and distinctly claim the subject matter which applicant regards as the invention. In Claim 40, as read into by Claim 1, the phrase "encoding a modified amino acid" is unclear. Modified amino acids are not encoded by genes, but are altered

after protein production; modified amino acid sequences may be the intended language. Clarification is required.

13. Claims 40, 42-43 and 45 are rejected under 35 U.S.C. § 112, second paragraph, as being indefinite for failing to particularly point out and distinctly claim the subject matter which applicant regards as the invention. In Claim 40, as read into by Claim 1, the phrase "capable of accelerating the biosynthesis of ML-236B" is unclear. SEQ ID NO:42 is described as a transcription factor that increases transcription of *mlc*A-D and *mlc*R (see page 71); this acceleration was assayed by RT-PCR which in no way assays for accelerated ML-236B production. Thus, it is unclear how this function is assigned to SEQ ID NO:42. The Examiner suggests rewriting the claim to limit the polypeptide, which is encoded by the polynucleotide in the vector used in the methods, to a function that increases transcription of *mlc*A-D and *mlc*R. Correction is required.

14. Claims 40-43 and 45 are rejected under 35 U.S.C. § 112, second paragraph, as being indefinite for failing to particularly point out and distinctly claim the subject matter which applicant regards as the invention. In Claim 40, as read into by Claim 27, the phrase "vector...obtained from... *E. coli* FERM BP-70006" is unclear. Is this vector specifically pSAKexpR? Or can this vector be any vector obtainable from the deposited *E. coli*? The claimed scope is unclear. The Examiner suggests rewriting the claim (into Claim 40) as ---A vector according to claim 26 that is pSAKexpR SANK 72599--- for clarity.

15. Claim 42 is rejected under 35 U.S.C. § 112, second paragraph, as being indefinite for failing to particularly point out and distinctly claim the subject matter which applicant regards as the invention. The phrase "wherein the vector comprises no additional genes is confusing considering the state of the art of transformation. Typically, marker genes, such as ampicillin resistance genes, are used in transformation to confirm insertion of the vector into the host cell. Such marker genes encode proteins that affect, for example, ampicillin resistance. Does this claim intend to exclude such markers from being on the vector used in the methods? Clarification is required.

16. Claim 43 is rejected under 35 U.S.C. § 112, second paragraph, as being indefinite for failing to particularly point out and distinctly claim the subject matter which applicant regards as the invention. In Claim 43, no distinction between recombinant mlcA protein and non-recombinant mlcA protein is understood in the art and/or in the specification. Perhaps the claim language should refer to recombinant genes? Clarification is required.

The following is a quotation of the first paragraph of 35 U.S.C. § 112:

> The specification shall contain a written description of the invention, and of the manner and process of making and using it, in such full, clear, concise, and exact terms as to enable any person skilled in the art to which it pertains, or with which it is most nearly connected, to make and use the same and shall set forth the best mode contemplated by the inventor of carrying out his invention.

17. Claims 40, 42, 43, and 45 are rejected under 35 U.S.C. § 112, first paragraph, written description, as containing subject matter which was not described in the specification in such a way as to reasonably convey to one skilled in the relevant art that the inventor(s), at the time the

application was filed, had possession of the claimed invention. Claim 40, by virtue of Claim 1, is drawn to methods using host cells containing vectors containing a polynucleotide that is a **variant** of a polynucleotide encoding SEQ ID NO:42 (mlcR), a transcription factor for the transcription of the *mlc*A-D genes of the ML-236B biosynthetic pathway. While this variant has function in the claim limitations (albeit an unclear function as noted above in the rejection under 35 U.S.C. § 112, second paragraph), this variant has no definite structural limitations by virtue of the unlimited amount of deletions, substitutions, and/or alterations with respect to a polynucleotide that encodes SEQ ID NO:42.

The Court of Appeals for the Federal Circuit has recently held that a "written description of an invention involving a chemical genus, like a description of a chemical species, 'requires a precise definition, such as be structure, formula [or] chemical name,' of the claimed subject matter sufficient to distinguish it from other materials." University of California v. Eli Lilly and Co., 1997 U.S. App. LEXIS 18221, at *23, quoting Fiers v. Revel, 25 USPQ2d 1601, 1606 (Fed. Cir. 1993) (bracketed material in original). To fully describe a genus of genetic material, which is a chemical compound, applicants must (1) fully describe at least one species of the claimed genus sufficient to represent said genus whereby a skilled artisan, in view of the prior art, could predict the structure of other species encompassed by the claimed genus and (2) identify the common characteristics of the claimed molecules, e.g., structure, physical and/or chemical characteristics, functional characteristics when coupled with a known or disclosed correlation between function and structure, or a combination of these.

In the instant specification, SEQ ID NO:42 (mlcR) is described as a transcription factor that enhances expression of the *mlc*A-D and *mlc*R genes. This transcription factor is described

as being used in methods to produce ML-236B and/or pravastatin. Only one species of mlcR is described. No common characteristics of mlcR and other transcription factors is described. Thus, without any definite structure, one of skill in the art would be unable to recognize other members of the claimed genus of methods. For these reasons, the instant claims are not adequately described. The Examiner notes that methods using a polynucleotide encoding exactly SEQ ID NO:42, using a polynucleotide that is exactly SEQ ID NO:41, and/or using the vector pSAXexpR all have adequate written description in the specification as originally filed.

18. Claims 40-43 and 45 are rejected under 35 U.S.C. § 112, first paragraph, enabling deposit, as containing subject matter which was not described in the specification in such a way as to enable one skilled in the art to which it pertains, or with which it is most nearly connected, to make and/or use the invention. To practice the instant methods, one of skill in the art is required to use FERM BP-7006 which is disclosed as containing pSAKexpR. While the instant specification contains limited deposit information, the requirements to enable such a deposit have not been fully met by the instant application. To enable the instant claims by enabling the deposit of DSM 12968, the following items are required: (1) the accession number assigned by the depository, (2) the date of deposit, (3) a brief description of the deposit, (4) **the name and full address of the depository** (37 C.F.R. § 1.801 - 1.809) (those which are in bold have not been fulfilled by the instant specification), **and** (5) the record must also contain a statement certifying that all restrictions on accessibility to said deposit be irrevocably removed by Applicant upon the granting of the patent (see M.P.E.P. § 2404.01); this statement may be certified by Applicants or Applicants' representative.

Reference to the deposit is found in the specification on pages 10 and 31; said reference is incomplete by virtue of the missing full address. The specification must be amended to correct this defect. Additionally, the record contains no statement certifying that all restrictions on accessibility to said deposit be irrevocably removed by Applicant upon the granting of the patent; said statement must be made.

19. Claims 40-43 and 45 are rejected under 35 U.S.C. § 112, first paragraph, scope of enablement, because the specification, while being enabling for methods using host cells that contain the biosynthetic pathway for ML-236B (for example, *P. citrinum*), does not reasonably provide enablement for methods using host cells that do not contain the biosynthetic pathway for ML-236B. The specification does not enable any person skilled in the art to which it pertains, or with which it is most nearly connected, to practice the invention commensurate in scope with these claims. To practice the claimed invention in, for example, *E. coli*, would require undue experimentation.

The factors to be considered in determining whether undue experimentation is required are summarized In re Wands 858 F.2d 731, 8 USPQ2nd 1400 (Fed. Cir, 1988). The Court in Wands states: "Enablement is not precluded by the necessity for some experimentation such as routine screening. However, experimentation needed to practice the invention must not be undue experimentation. The key word is 'undue,' not 'experimentation.' " (Wands, 8 USPQ2d 1404). Clearly, enablement of a claimed invention cannot be predicated on the basis of quantity of experimentation required to make or use the invention. "Whether undue experimentation is needed is not a single, simple factual determination, but rather is a conclusion reached by weighing many factual considerations." (Wands, 8 USPQ2d 1404). The factors to be considered

in determining whether undue experimentation is required include: (1) the quantity of experimentation necessary, (2) the amount or direction or guidance presented, (3) the presence or absence of working examples, (4) the nature of the invention, (5) the state of the prior art, (6) the relative skill of those in the art, (7) the predictability or unpredictability of the art, and (8) the breadth of the claims. While all of these factors are considered, a sufficient amount for a *prima facie* case is discussed below.

In the instant specification, the only working examples with *mlcR* involve its transformation into *P. citrinum*. While ML-236B production was not measured in these experiments, transcription of ML-236B biosynthetic genes was increased; thus it follows that ML-236B would be produced in such cells, likely at a higher rate. However, no examples of mlcR, or any ML-236B biosynthetic proteins, functioning outside its native *P. citrinum* is described in the instant specification or the art. The ability to recreate this polyketide production system in host cells other than *P. citrinum* is wholly unpredictable as evidenced in the polyketide synthase (PKS) field which requires numerous accessory proteins as well as a supply of appropriate precursors not usually found in non-polyketide producing cells to function in, for example, *E. coli* host cells. No guidance has been offered in the instant specification to meet this end. Thus, the instant claims are not enabled to the full extent of their scope.

Claim Rejections - 35 U.S.C. § 102

The following is a quotation of the appropriate paragraphs of 35 U.S.C. § 102 that form the basis for the rejections under this section made in this Office action:

> A person shall be entitled to a patent unless –
>
> (a) the invention was known or used by others in this country, or patented or described in a printed publication in this or a foreign country, before the invention thereof by the applicant for a patent.

20. Claims 40, 42-43 and 45 are rejected under 35 U.S.C. § 102(a) as being anticipated by WO 2001/12814 (see IDS #8). The instant claims are drawn to methods of producing ML-236B in a host cell that has been transformed with a polynucleotide encoding a variant of SEQ ID NO:42.

WO 2001/12814 teaches a 34203 base pairs gene cluster that, when transformed into *P. citrinum*, produces ML-236B. Said gene cluster contains a variant of SEQ ID NO:42 (see attached alignment).

Other Relevant Art

21. The following are cited for completeness of the record:

a) Abe *et al.* Molecular cloning and characterization of an ML-236B (compactin) biosynthetic gene cluster in *Penicillium citrinum*. Mol Genet Genomics 2002 Jul;267(5):636-46.
b) Abe *et al.* Effect of increased dosage of the ML-236B (compactin) biosynthetic gene cluster on ML-236B production in *Penicillium citrinum*. Mol Genet Genomics 2002 Sep;268(1):130-7.
c) Abe *et al.* Functional analysis of mlcR, a regulatory gene for ML-236B (compactin) biosynthesis in *Penicillium citrinum*. Mol Genet Genomics 2002 Nov;268(3):352-61.

Conclusion

22. Claims 40-43 and 45 are rejected for the reasons identified in the numbered sections of this Office action. Applicants must respond to the objections/rejections in each of the numbered sections in this Office action to be fully responsive in prosecution.

Any inquiry concerning this communication or earlier communications from the examiner should be directed to Kathleen M Kerr whose telephone number is (703) 305-1229. The examiner can normally be reached on Monday through Friday, from 8:30am to 5pm.

If attempts to reach the examiner by telephone are unsuccessful, the examiner's supervisor, Ponnathupura Achutamurthy can be reached on (703) 308-3804. The fax phone numbers for the organization where this application or proceeding is assigned are (703) 872-9306 for regular communications and (703) 872-9307 for After Final communications.

Any inquiry of a general nature or relating to the status of this application or proceeding should be directed to the receptionist whose telephone number is (703) 308-0196.

KMK
May 27, 2003